REMARKS

Claims 1, 2, 4, 5, 7-11, 13-16, 18, 19 and 21-28 were pending in the application. Claims 4, 7, 10, and 13 have been amended to correct for dependencies. Thus, upon entry of this Amendment, claims 1, 2, 4, 7-11, 13-16, 18, 19, and 21-28 are pending in the application.

No new matter has been added. Applicants request that the amendments to the specification and claims be entered. The foregoing claim amendments and cancellation should in no way be construed as an acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the present application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Double Patenting Rejection of Claims 1-11 and 13-28

Claims 1-11 and 13-28 are rejected under the judicially created doctrine of nonstatutory obvious-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 5,866,755. Applicants request that the Examiner hold the double-patenting rejection in abeyance until the claimed subject matter is indicated allowable.

Information Disclosure Statement

The Examiner has indicated that the Information Disclosure Statement (IDS) filed on August 23, 1999 could not be located. Applicants provide herewith a copy of the paperwork which was submitted with the IDS filed on August 23, 1999, along with a copy of the date-stamped postcard indicating receipt by the U.S. Patent Office. In accordance with the previously filed IDS, Applicants also submit herewith copies of some of the references listed in previously submitted Attachment C. Applicants were unable to obtain copies of all of the previously submitted references to be filed with this response, and will submit them in due course. Applicants point out that the references attached in Appendices A and B of said IDS were previously submitted in corresponding parent applications, and thus do not need to be resubmitted.

Rejection of Claims 1, 2, 4, 5, 7-11, 13-16, 18, 19, and 21-28 Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4, 5, 7-11, 13-16, 18, 19, and 21-28 are rejected as containing subject matter which is not described in the specification in such a way as to enable one of ordinary skill in the art to make or use the claimed invention. The Examiner states that "the phenotype(s) of the claimed animals cannot be predicted because the art of making transgenic animals or knockout animals is highly unpredictable." Applicants respectfully traverse this rejection.

The invention is directed to a non-human transgenic organism having a transgene comprising a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, the fusion protein comprising a first polypeptide which is a Tet repressor or mutated Tet repressor that binds to a *tet* operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells.

The invention also relates to a non-human transgenic animal having a transgene comprising a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, wherein the fusion protein comprises a first polypeptide which is a Tet repressor or a mutated Tet repressor that binds to a *tet* operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells, wherein the transgene is integrated by at a predetermined location within a chromosome within cells of the animal.

The invention also includes a non-human transgenic animal having a transgene integrated into the genome of the animal and also having a *tet* operator-linked gene in the genome of the animal, wherein the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said *tet* operator linked gene, said fusion protein comprises a first polypeptide that is a Tet repressor or a mutated Tet repressor operably linked to a heterologous second polypeptide which inhibits transcription of said *tet* operator-linked gene in eucaryotic cells, said *tet* operator-linked gene confers a detectable and functional phenotype on the animal when expressed in cells of the animal, said transgene is expressed in cells of the animal at a level sufficient to

produce amounts of said fusion protein that are sufficient to inhibit transcription of the *tet* operator-linked gene, and in the absence or presence of tetracycline or a tetracycline analogue in the animal, said fusion protein binds to the *tet* operator-linked gene and inhibits transcription of the *tet* operator linked gene, wherein the level of expression of the *tet* operator-linked gene can be upregulated by administering or depleting tetracycline or a tetracycline analogue to the animal.

While the Examiner acknowledges that the specification is enabling for a transgenic mouse comprising the tetracycline-based transcriptional regulatory system of the invention, the Examiner is of the opinion that the specification is not enabling for non-human transgenic animals in view of the unpredictability of the art. The Examiner cites the Wood reference in support of the notion that the phenotype of transgenic animals cannot be predicted. Wood provides general guidelines for evaluating transgenic phenotypes (see pages 12-13, sections entitled "General Paradigm for Phenotype Assessment" and "Secondary Level Assessment: Quantify and Evaluate Abnormalities"), noting the "growing interest in phenotype assessment of large numbers of mice" to be used as research tools as model systems. For example, Wood teaches that one of ordinary skill in the art should consider the effects of genetic background and the environment when examining the resulting phenotype of a transgenic animal.

Wood supports the use of transgenic animals as models for human disease, and, contrary to the Examiner's assertion, does not "clearly indicate[s] that the phenotype of a transgenic mouse or rat or any animal cannot be predicted." Wood notes, as quoted by the Examiner, that sometimes ordinarily skilled artisans incorrectly predict a phenotype based on current knowledge of a particular gene, however this is not a general disclaimer that the phenotypes of transgenic animals are impossible to predict. Applicants submit that the scientific process calls for one to make an educated scientific estimation of the expected result which may or may not be correct upon completion of the experiment. Importantly, as described in more detail below, it should be noted that the process of making a non-human transgenic animal requires an initial litter of non-human transgenic animals to be screened in order to identify founders who are then used to propagate a transgenic line. For example, if the transgenic non-human animal contained a gene which caused obesity, one of ordinary skill in the art would identify non-human

transgenic animals carrying the gene with a propensity for increased weight over those animals with the gene who do not exhibit an obese phenotype.

In addition, ***Applicants submit that the "phenotype" which the Examiner and Wood are referring is dependent upon the gene of interest which is operatively linked to the tet operator in the transgenic non-human animal of the invention***. Expression of the *tet* operator linked gene confers a detectable and functional phenotype on the animal when expressed in the cells of the animal. For example, at pages 61 to 63 of the instant specification, Applicants teach that the detectable and functional phenotype of transgenic mice comprising a luciferase reporter gene operably linked to the *tet* operator is an increase in luciferase activity resulting from the expression of the luciferase gene.

Applicants provide a transgenic non-human animal comprising a highly regulatable gene expression system, wherein a transgene comprising a fusion protein comprising a Tet repressor or a mutated Tet repressor is fused to a transcriptional inhibitor and is integrated into the genome of the non-human transgenic animal. The fusion protein in turn inhibits or allows for the transcription of a gene which is operably linked to a *tet* operator through the presence or absence of tetracycline or a tetracycline analogue, thus providing a consistent and predictable regulatory system. Importantly, the claimed non-human transgenic animals do not rely on endogenous transcriptional activators and/or inhibitors to control expression of the gene of interest. Furthermore, transcriptional control is regulated by the presence of an effector molecule (tetracycline or a tetracycline analogue) and does not rely on an endogenously produced effector which may or may not be present in the cell.

In Applicants' previous response of December 8, 1999, a number of scientific publications were submitted in support of Applicants' position that transgenic animals comprising an exogenous gene had been successfully produced at the time the invention was made, and that it was routine in the art at the time the invention was made to produce transgenic animals other than mice, including pigs, sheep, and goats. The previously submitted references include the following:

Pursel *et al.* (1990), who teach the production of transgenic pigs which express bovine and human growth hormone (previously submitted Appendix I);

Rexroad *et al.* (1991), who teach the production of transgenic sheep expressing bovine or human growth factor-releasing hormone (previously submitted Appendix J); and Ebert *et al.* (1991), who teach the production of transgenic goats expressing a human tissue-type plasminogen activator (previously submitted as Appendix K).

In addition to those described above, Applicants provide the following references to further support that transgenic non-human animals other than mice had been created at the time the invention was made:

L and M. WO 92/22646 and WO 93/25017, entitled "Production of Human Hemoglobin Transgenic Pigs" (attached herewith as Appendix L and M, respectively; hereinafter referred to as '646 and '071, respectively) teach the production of transgenic pigs expressing the human hemoglobin gene.

N. U.S. patent no. 5,366,894, entitled "Protein Production" (attached herewith as Appendix N; hereinafter referred to as '894) teaches a method of producing transgenic sheep who express a desired transgene in their milk, wherein the protein can be easily collected and purified.

O. Fodor *et al.* (1994) *PNAS* 91:11153-11157 (attached herewith as Appendix O; hereinafter referred to as "Fodor") who describe the production of transgenic pigs which express human CD59;

P. Kroshus *et al.* (1996) *Transplantation* 61:1513-1521 (attached herewith as Appendix P; hereinafter referred to as "Kroshus") who describe transgenic pigs who express human CD59 on their organs in order to decrease the chance of rejection in xenotransplantation. The Kroshus paper follows the experiment described in the above-mentioned Fodor publication, and demonstrates that the transgenic pigs originally described in Fodor were successfully used in subsequent studies;

Q. Wall *et al.* (1996) *Transgenic Research* 5:67-72 (attached herewith as Appendix Q; hereinafter referred to as "Wall") who describe transgenic sheep which express the whey acidic protein (WAP); and

R. PCT publication no. WO 97/19589 (attached herewith as Appendix R; hereinafter referred to as '589) teaches methods of producing transgenic goats, including how to obtain goat stem cells.

Applicants point out to the Examiner that it is common practice in the production of transgenic non-human animals to first examine the initial litter or group of potential transgenic animals in order to determine which of the first generation has the transgene integrated into the animal's genome. From this initial litter of animals, a population of transgenic organisms is identified and is referred to as the "founders," wherein each animal potentially has a different genetic identity, *i.e.*, number of copies of the transgene, different integration sites, etc., from which the desired "founder" animal(s) will be selected. As described in the working example of the instant specification, as well as in the above-mentioned publications, founder transgenic animals can display different characteristics of the transgene depending on, for example, integration site within the genome, including the "position effect," number of copies of the transgene, etc. These differences are recognized by the ordinarily skilled artisan through known nucleic acid assays which examine the transgene properties, such as PCR (see instant specification, Example 1), Northern blot analysis (see Wall), and DNA slot blot analysis (see Fodor). As taught by Applicants in the working example, each of the founder transgenic animals can be analyzed to determine the transgene expression in correlation with the phenotype. Identified "founder animals" are then selected for breeding, as taught by Applicants, in order to "breed additional animals carrying the transgene" and to produce transgenic animals displaying the desired phenotype and transgene expression (see page 18, lines 12-15 of instant specification). For example, in Kroshus, three founder piglets were identified where one piglet was found to have 10-20 copies of the transgene, while the other two piglets had only about one copy of the transgene and showed very little and inconsistent transgene expression. The founder piglet with 10-20 copies was used to produce a transgenic line of piglets, which had a predictable and consistent phenotype, *i.e.*, high level cell surface expression of hCD59. The founder piglet was subsequently used for further analysis of the transgenic pigs comprising the human hCD59 gene, as described in Kroshus. Thus, Applicants submit that while the initial litter of transgenic animals had different transgene and phenotypic characteristics, those with the desired characteristics can be chosen to act as founders in the production of a transgenic line of non-human animals with predictable and consistent phenotypes.

The Examiner cites MPEP 2164.03 in support of his position regarding predictability in the art. MPEP 2164.03 states, "[t]he more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification." Applicants maintain that the methodologies taught in the instant specification regarding the production of transgenic animals, as well as the general knowledge (as exemplified by the references submitted herewith and in the response filed on December 8, 1999), fully support the claimed invention, specifically non-human transgenic animals, including sheep, pigs, goats, and cows. Applicants also maintain that the predictability described by the Examiner is dependent upon the selected gene of interest which induces a phenotype. The working examples of the specification demonstrate that the claimed tetracycline gene expression regulatory system produces predictable and consistent gene expression.

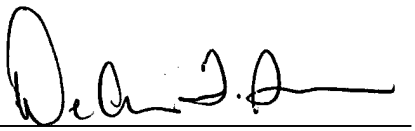
In view of the arguments presented above, Applicants submit that the specification meets the enablement requirement and Applicants thus respectfully request that the rejection of claims 1, 2, 4, 5, 7-11, 13-16, 18, 19, and 21-28 under U.S.C. § 112 first paragraph, be withdrawn.

SUMMARY

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested.

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,



DeAnn F. Smith, Esq.
Reg. No. 36,683
Attorney for Applicant

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Dated: September 22, 2003

LAHIVE
&
COCKFIELD
LLP

COUNSELLORS AT LAW
28 STATE STREET
BOSTON, MASSACHUSETTS 02109-1784
TELEPHONE (617) 227-7400
FAX (617) 742-4214
lc@lahcoc.com

August 20, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Patent Application No.: 09/241,347
ANIMALS TRANSGENIC FOR A TETRACYCLINE REGULATED TRANSCRIPTIONAL INHIBITOR
Inventors: Herman Bujard et al.
Filed: February 2, 1999
Our Ref. No.:BBI-009C4CN

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Information Disclosure Statement;
2. PTO Forms 1449 (Attachments A-C);
3. Copies of references (39) cited in PTO Form 1449 (Attachment C);
4. A check for $240.00; and
5. A Return Postcard

No additional costs are believed to be due in connection with the filing of this Information Disclosure Statement. However, please charge any necessary fees in connection with the enclosed statement to our Deposit Order Account No. 12-0080. For this purpose, a duplicate of this sheet is attached.

I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on:

8/20/99
Date

Amy E. Mandragouras, Reg. 36,207

Respectfully submitted,
LAHIVE & COCKFIELD, LLP

Amy E. Mandragouras, Reg. 36,207
for Elizabeth A. Hanley, Reg. 33,505
Attorney for Applicants

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Hermann Bujard and Manfred Gossen Serial No.: 09/241,347 Filed: February 2, 1999 For: *ANIMALS TRANSGENIC FOR A TETRACYCLINE-REGULATED TRANSCIPTIONAL INHIBITOR* Attorney Docket No.: BBI-009C4CN	Group Art Unit: 1632 Examiner: Shukla, R.

Assistant Commissioner for Patents
Washington, D.C. 20231

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8/20/99
Date of Signature and of Mail Deposit

By: _____
Amy E. Mandragouras, Reg. 36,207

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicants and their attorney are aware of the following publications and information, listed on the *three* attached PTO Forms 1449 (Attachments A-C) in accordance with 37 CFR §1.97. A copy of each cited publication in Attachments A and B was filed in the parent case U.S. Serial No. 08/486,814, filed on June 7, 1995, now issued as U.S. Patent No. 5,866,755, and relied upon for an earlier filing date Under 35

U.S.C. 120. Applicants hereby submit those publications from related applications which were not cited in the parent application, as set forth in a *third* PTO Form 1449 (Attachment C).

This statement is not to be interpreted as a representation that the cited publications are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any publication herein be construed *per se* as a representation that such publication is prior art. Moreover, Applicants understand that the Examiner will make an independent evaluation of the cited publications.

Inasmuch as this Information Disclosure Statement is being filed after July 8, 1999, the mailing date of the first Office Action in the instant application, a check for the $240.00 fee pursuant to 37 C.F.R. section 1.17(p) is enclosed. Please credit any overpayment or deduct any underpayment to our Deposit Order Account No. 12-0080. For this purpose, a copy of this statement is also enclosed.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

Amy E. Mandragouras, Reg. 36,207 for
Elizabeth A. Hanley, Reg. 33,505
Attorney for Applicants

28 State Street
Boston, MA 02109
(617) 227-7400
Date: 7/20/99
GAD/EAH/JLE/ipc

Office No. BBI-009C4CN

THE "RECEIVED" STAMP OF THE PATENT AND TRADEMARK OFFICE IMPRINTED HEREON ACKNOWLEDGES THE FILING OF:

Description of Paper* : Transmittal Letter (in duplicate), Information Disclosure Statement, PTO Forms 1449 (3 pages of Attachment A; 2 pages of Attachment B; and 2 pages of Attachment C); copies of publications cited therein (39); check for $240.00 (fee for filing of IDS after issuance of first Office Action); are enclosed along with this postcard.

Title: *ANIMALS TRANSGENIC FOR A TETRACYCLINE REGULATED TRANSCRIPTIONAL*

Name of Applicants: Bujard, H. and Gossen, M.

Serial No.: 09/241,347

Atty: Elizabeth A. Hanley

Date: August 20, 1999

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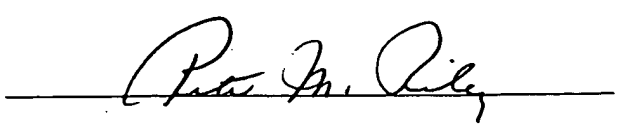

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Attachment A

Sheet 1 of 3

APPLICANT FACSIMILE OF FORM PTO-1449 REV 7-80 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY DOCKET NO.	SERIAL NO.
LIST OF PUBLICATIONS CITED BY APPLICANT (Use several sheets if necessary)	BBI-009C4CN	09/241,347
	APPLICANT: Hermann Bujard and Manfred Gossen	
	FILING DATE: February 2, 1995	GROUP: 1632

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	5,221,778	6/93	Byrne et al.	800	2	
	AB	4,833,080	05/89	Brent et al.	435	172.3	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AC	WO 94/04672	03/94	PCT				
	AD	WO 92/20808	11/92	PCT				
	AE	WO 91/19784	12/91	PCT				
	AF	WO 93/04169	03/93	PCT				
	AG	WO 91/19796	12/91	PCT				
	AH	WO 92/11874	07/92	PCT				
	AI	EP 0 332 416	09/89	EPO				
	AJ	WO 93/23431	11/93	PCT				
	AK	WO 94/18317	08/94	PCT				
	AL	0 455 687 B1	11/91	EPO				
	AM	0 455 424 A2	11/91	EPO				
	AN	0 494 724 A2	07/92	EPO				

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

	AO		Hinrichs, W., et al., (1994) "Structure of the Tet Repressor-Tetracycline Complex and Regulation of Antibiotic Resistance", *Science*, Vol. 264, pp. 418-420;
	AO'		Hecht, B., et al., (1993) "Noninducible Tet Repressor Mutations Map from the Operator Motif to the C Terminus", *Journal of Bacteriology*, Vol. 175, No. 4;
	AP		Gossen, M., et al., (1993) "Control of gene activity in higher eukaryotic cells by prokaryotic regulatory elements", *TIBS*, Vol. 18, No. 12, pp. 471-475;
	AQ		Fieck, A., et al., (1992) "Modification of the *E. Coli* Lac Repressor for Expression in Eukaryoitic Cells: Effect of Nuclear Signal Sequence on Protein Activity and Nuclear Documentation", *Nucleic Acid Research*, Vol. 20, pp. 1785-1791;
	AR		Seipel, K., et al., (1992) "Different activation domains stimulate transcription from remote ('enhancer') and proximal ('promoter') positions", *The EMBO Journal*, Vol. 11, No. 13, pp. 4961-4968;
	AS		Epstein-Baak, R., et al., (1992) "Inducible Transformation of Cells from Transgenic Mice Expressing SV40 under *Lac* Operon Control", *Cell Growth & Differentiation*, Vol. 3, pp. 127-134;
	AT		Gossen, M., and Bujard, H., (1992) "Tight control of gene expression in mammalian cells by tetracycline-responsive promoters", *Proceedings of the National Academy of Science*, Vol. 89, pp. 5547-5551;
	AU		Bradley, A., (1991) "Modifying the mammalian genome by gene targeting", *Current Opinion in Biotechnology*, Vol. 2, pp. 832-829;
	AV		Wyborski, D.L., and Short, J.M., (1991) "Analysis of Inducers of the *E. Coli* Lac Repressor System in Mammalian Cells and Whole Animals", *Nucleic Acid Research*, Vol. 19, pp. 4647-4653;

Examiner	Date Considered

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

APPLICANT FACSIMILE OF FORM PTO-1449 REV 7-80 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY DOCKET NO.	SERIAL NO.
LIST OF PUBLICATIONS CITED BY APPLICANT (Use several sheets if necessary)	BBI-009C4CN	09/241,347
	APPLICANT: Hermann Bujard and Manfred Gossen	
	FILING DATE: February 2, 1995	GROUP: 1632

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

	BA		Degenkolb, J., et al., (1991) "Structural Requirements of Tetracycline-Tet Repressor Interaction: Determination of Equilibrium Binding Constants for Tetracycline Analogs with the Tet Repressor", *Antimicrobial Agents and Chemotherapy*, Vol. 35, No. 8, pp. 1591-1595;
	BB		Baim, S.B., et al., (1991) "A chimeric mammalian transactivator based on the *lac* repressor that is regulated by temperature and isopropyl β-D-thiogalactopyranoside", *Proceedings of the National Academy of Science*, Vol. 88, pp. 5072-5076;
	BC		Gatz, C., et al., (1991) "Regulation of a modified CaMV 35S promoter by the Tn *10*-encoder Tet receptor in transgenic tobacco", *Mol. Gen. Genet.*, Vol. 227, No. 2, pp. 229-237;
	BD		Wissmann, A., et al., (1991) "Selection for Tn*10* Tet Repressor Binding to *tet* Operator in *Escherichia coli*: Isolation of Temperature-Sensitive Mutants and Combinatorial Mutagenesis in the DNA Binding Motif", *Genetics*, Vol. 128, pp. 225-232;
	BE		Labow, M.A., et al., (1990) "Conversion of the *lac* Repressor into an Allosterically Regulated Transcriptional Activator for Mammalian Cells", *Molecular and Cellular Biology*, Vol. 10, No. 7, pp. 3343-3356;
	BF		Deuschle, U., et al., (1989) "Regulated expression of foreign genes in mammalian cells under the control of coliphage T3 RNA polymerase and *lac* repressor", *Proceedings of the National Academy of Science*, Vol. 86, pp. 5400-5404;
	BG		Capecchi, M.R., (1989) "Altering the Genome by Homologous Recombination", *Science*, Vol. 244, pp. 1288-1292;
	BH		Mermod, N., et al., (1989) "The Proline-Rich Transcriptional Activator of CTF/NF-I Is Distinct from the Replication and DNA Binding Domain", *Cell*, Vol. 58, 741-753;
	BI		Mansour, S.L., et al., (1988) "Disruption of the proto-oncogene *int*-2 in mouse embryo-derived stem cells: a general strategy for targeting mutations to non-selectable genes", *Nature*, Vol. 336, pp. 348-352;
	BJ		Gatz, C., and Quail, P.H., (1988) "Tn*10*-encoded *tet* repressor can regulate an operator-containing plant promoter", *Proceedings of the National Academy of Science*, Vol. 85, pp. 1394-1397;
	BK		Figge, J., et al., (1988) "Stringent Regulation of Stably Integrated Chloramphenicol Acetyl Transferase Genes by *E. coli lac* Repressor in Monkey Cells", *Cell*, Vol. 52, 713-722;
	BL		Triezenberg, S.J., et al., (1988) "Functional dissection of VP16, the *trans*-activator of herpes simplex virus immediate early gene expression", *Genes & Development*, Vol. 2, pp. 718-729;
	BM		Courey, A.J., and Tjian, R., (1988) "Analysis of Sp1 *In Vivo* Reveals Multiple Transcriptional Domains, Including a Novel Glutamine-Rich Activation Motif", *Cell*, Vol. 55, pp. 887-898;
	BN		Tovar, K., et al., (1988) "Identification and nucleotide sequence of the class E *tet* regulatory elements and operator and inducer binding of the encoded purified Tet repressor", *Mol. Gen. Genet.*, Vol. 215, pp. 76-80;
	BO		Altschmied, L. et al., (1988) "A threonine to alanine exchange at position 40 of Tet repressor alters the recognition of the sixth base pair of *tet* operator from GC to AT", *The EMBO Journal*, Vol. 7, No. 12, pp. 4011-4017;
	BP		Brown, M., et al., (1987) "*lac* Repressor Can Regulate Expression from a Hybrid SV40 Early Promoter Containing a *lac* Operator in Animal Cells", *Cell*, Vol. 49, pp. 603-612;
	BQ		Hu,M.C-T and Davidson, N., (1987) "The Inducible *lac* Operator-Repressor System Is Functional in Mammalian Cells", *Cell*, Vol. 46, pp. 555-566;
	BR		Smithies, O., et al., (1985) "Insertion of DNA sequences into the human chromosomal β-globin locus by homologous recombination", *Nature*, Vol. 317, pp. 230-234;
	BS		Boshart, M., et al., (1985) "A Very Strong Enhancer Is Located Upstream of an Immediate Early Gene of Human Cytomegalovirus", *Cell*, Vol. 41, No. 2, pp. 521-530;
	BT		Postle, K., et al., (1984) "Nucleotide sequence of the repressor gene of the TN*10* tetracycline resistance determinant", *Nucleic Acid Research*, Vol. 12, No. 12, pp. 4849-4863;
	BU		Unger, B., et al., (1984) "Nucleotide sequence of the gene, protein purification and characterization of the pSC101-encoded tetracycline resistance-gene-repressor", *Gene*, Vol. 31, pp. 103-108;

Examiner	Date Considered

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

APPLICANT FACSIMILE OF FORM PTO-1449 REV 7-80 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY DOCKET NO.	SERIAL NO.
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	APPLICANT: Hermann Bujard and Manfred Gossen	
	FILING DATE: February 2, 1995	GROUP: 1632

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

	CA		Unger, B., et al., (1984) "Nucleotide sequence of the repressor gene of the RA1 tetracycline resistance determinant: structural and functional comparison with three related Tet repressor genes", *Nucleic Acid Research*, Vol. 12, No. 20, pp. 7693-7703;
	CB		Waters, S.H, et al., (1983) "The tetracycline resistance determinants of RP1 and Tn*1721*: nucleotide sequence analysis", *Nucleic Acid Research*, Vol. 11, No. 17, pp. 6089-6105;
	CC		Hillen, W., and Schollmeier, K., (1983) "Nucleotide sequence of the Tn*10* encoded tetracycline resistance gene", *Nucleic Acid Research*, Vol. 11, No. 2, pp. 525-539;
	CD		Brent, R. and M. Ptashne (1984) "A Bacterial Repressor Protein or a Yeast Transcriptional Terinator Can Block Upstream Activation of A Yeast Gene" *Nature* 312:612-615;
	CE		Brent R. and M. Ptashne (1985) "A Eukaryotic Transcriptional Activator Bearing the DNA Specificity of a Prokaryotic Repressor" *Cell* 43:729-736;
	CF		Baniahmad, A. et al. (1992) "A Transferable Silencing Domain Is Present In the Thyroid Hormone Receptor, In the v-erbA Oncogene Product and In the Retinoic Acid Receptor" *The EMBO Journal* 11(3):1015-1023;
	CG		Sauer, F. and H. Jäckle (1993) "Dimerization and the Control of Transcription by Krüppel" *Nature* 364:454-457;
	CH		Licht, J. et al. (1990) "Drosophila Krüppel Protein is a Transcriptional Repressor" *Nature* 346:76-79;
	CI		Herschbach B. and A. Johnson (1993) "Transcriptional Repression In Eukaryotes" *Annu. Rev. Cell Biol.* 9:479-509;
	CJ		Renkawitz R. (1990) "Transcriptional Repression In Eukaryotes" *TIG* 6(6):192-193;
	CK		Resnitzky D. (1994) "Acceleration of the G1/S Phase Transition by Expression of Cyclins D1 and E with an Inducible System" *Molecular and Cellular Biology* 14(3):1669-1679;
	CL		Furth P. (1994) "Temporal Control of Gene Expression in Transgenic Mice By A Tetracycline-Responsive Promoter" *Proc. Natl. Acad. Sci. USA* 91:9302-9306;
	CM		Wimmel A. et al. (1994) "Inducible Acceleration of G1 Progression Through Tetracycline-Regulated Expression of Human Cyclin E" *Oncogene* 9:995-997
	CN		Ackland-Berglund, C.E. and Leib, D.A.. (1995) "Efficacy of Tetracycline-Controlled Gene Expression Is Influenced by Cell Type" *BioTechniques* 18(2):196-200;
	CO		Gossen M. and B. Hermann (1993) "Anhydrotetracycline, A Novel Effector of Tetracycline Controlled Gene Expression Systems In Eukaryotic Cells" *Nucleic Acids Research* 21(18):4411-4412;
	CP		Buckbinder L. et al. (1994) "Gene Regulation by Temperature-Sensitive p53 Mutants: Identification of p53 response genes" *Proc. Natl. Acad. Sci. USA* 91:10640-10644;
	CQ		Yarranton G. (1992) "Inducible Vectors For Expression In Mamalian Cells" *Current Opinion in Biotechnology* 3:506-511;
	CR		Gossen et al. (1994) "Inducible Gene Expression Systems For Higher Eukaryotic Cells" *Current Opinion in Biotechnology* 5:516-520;
	CS		Weinmann P. et al. (1994) "A Chimeric Transactivator Allows Tetracycline-Responsive Gene Expression in Whole Plants" *The Plant Journal* 5(4):559-569;
	CT		Pescini R. et al. (1994) "Inducible Inhibition of Eukaryotic Gene Expression" *Biochemical and Biophysical Research Communications* 202(3):1664-1667;
	CU		Fishman G. et al. (1994) "Tetracycline-Regulated Cardiac Gene Expression in Vivo" *J. Clin. Invest.* 93:1864-1868;

Examiner	Date Considered

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APPLICANT FACSIMILE OF FORM PTO-1449 REV 7-80	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY DOCKET NO.	SERIAL NO.
LIST OF PUBLICATIONS CITED BY APPLICANT (Use several sheets if necessary)		BBI-009C4CN	09/241,347
		APPLICANT: Hermann Bujard and Manfred Gossen	
		FILING DATE: February 2, 1999	GROUP: 1632

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AB	WO 94/29442	12/94	PCT				

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

	AC		Cowell, "Repression versus activation in the control of gene transcription," *Trends in Biochemical Sciences*, 19:1, 38-42 (1994);
	AD		Deuschle et al., "Tetracycline-reversible silencing of eukaryotic promoters," *Mol. Cell. Biol.*, 15:4, 1907-1914 (1995);
	AE		Gatz et al., "Stringent repression and homogeneous de-repression by tetracycline of a modified CaMV 35S promoter in intact transgenic tobacco plants," *The Plant Journal*, 2:3, 397-404 (1992);
	AF		Gossen et al., "Exploiting prokaryotic elements for the control of gene activity in higher eukaryotics," Keystone Symposium on Gene Therapy and Molecular Medicine, Steamboat Springs, Colorado, *Journal of Cellular Biochemistry*, Supplement 0 (21A), Abstract no. C6-220, 355 (1995);
	AG		Gossen et al., "Transcriptional activation by tetracyclines in mammalian cells," *Science*, 268:5218, 1766-1769 (1995);
	AH		Liang et al., "Enhanced and switchable expression systems for gene-transfer," Keystone Symposium on Gene Therapy and Molecular Medicine, Steamboat Springs, Colorado, *Journal of Cellular Biochemistry*, Supplement 0 (21A), Abstract no. C6-220, 379 (1995).
	AI		Agarwal, M.L. et al., "p53 Controls Both the G_2/M and the G_1 Cell Cycle Checkpoints and Mediates Reversible Growth Arrest in Human fibroblasts," *Proc. Natl. Acad. Sci. USA*, 92: pp. 8493-8497 (1995);
	AJ		Bergman, M. et al. "Overexpressed Csk Tyrosine Kinase Is Localized in Focal Adhesions, Causes Reorganization of $\alpha_V\beta_5$ Integrin, and Interferes with HeLa Cell Spreading", *Molecular and Cellular Biology*, 15, No. 2, pp. 711-722 (1995);
	AK		Cayrol, C. et al. "Identification of Cellular Target Genes of the Epstein-Barr Virus Transactivator Zta: Activation of Transforming Growth Factor βigh3 (TGF-βigh3) and TGF-β1", *Journal of Virology*, 69, No. 7, pp. 4206-4212, (1995);
	AL		Chen, Y.Q. et al. "Tumor Suppression by *p21*^{WAF11}", *Cancer Research*, 55, pp. 4536-4539, (1995);
	AM		Dhawan, J. et al. "Tetracycline-Regulated Gene Expression Following Direct Gene Transfer into Mouse Skeletal Muscle", *Somatic Cell and Molecular Genetics*, 21, No. 4, pp. 233-240, (1995);

Examiner	Date Considered

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FOREIGN PATENT DOCUMENTS

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OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

	AN		Efrat, S. et al. "Conditional Transformation of a Pancreatic β-Cell Line Derived From Transgenic Mice Expressing A Tetracycline-Regulated Oncogene" *Proc. Natl. Acad. Sci. USA*, 92, pp. 3576-3580 (1995);
	AO		Gjetting, T. et al. "Regulated Expression of the Retinoblastoma Susceptibility Gene in Mammary Carcinoma Cells Restores Cyclin D1 Expression and G_1-Phase Control", *Biol. Chem. Hoppe-Seyler*, 376, pp. 441-446 (1995);
	AP		Haase, S.B. et al. "Transcription Inhibits the Replication of Autonomously Replicating Plasmids in Human Cells", *Molecular and Cellular Biology*, 14, No. 4, pp. 2516-2524 (1994);
	AQ		Hennighausen, L. et al. "Conditional Gene Expression in Secretory Tissues and Skin of Transgenic Mice Using the MMTV-LTR and the Tetracycline Responsive System", *Journal of Cellular Biochemistry*, 59, pp. 463-472, (1995);
	AR		Howe, J.R. et al. "The Responsiveness of a Tetracycline-Sensitive Expression System Differs in Different Cell Lines", *The Journal of Biological Chemistry*, 270, No. 23, pp. 14168-14174, (1995);
	AS		Miller, K. et al. "The Function of Inducible Promoter Systems in F9 Embryonal Carcinoma Cells", *Experimental Cell Research*, 218, pp. 144-150, (1995);
	AT		Passman, R.S. et al., "Regulated Expression of Foreign Genes In Vivo After Germline Transfer", *J. Clin. Invest.*, 94, pp. 2421-2425 (1994)
	AU		Sopher, B.L. et al., "Cytotoxicity Mediated By Conditional Expression of a Carboxyl-Terminal Derivative of the β-Amyloid Precursor Protein", *Molecular Brain Research*, 26, pp. 207-217, (1994);
	AV		Wu, Z. et al. "Conditional Ectopic Expression of C/EBPβ in NIH-3T3 Cells Induces PPARγ and Stimulates Adipogenesis", *Genes & Development*, 9, pp. 2350-2363, (1995).

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		APPLICANT: Bujard, H. and Gossen, M.	
		FILING DATE: 02/02/99	GROUP: 1632

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	DA	5,464,758	11/95	Gossen et al.	435	69.1	
	DB	5,545,808	8/96	Hew et al.	800	2	
	DC	5,595,895	1/97	Miki et al.	435	172.3	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	DD	WO 96/01313	01/96	PCT				
	DE	WO 91/13979	9/91	PCT				

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

	DF		Ackland-Berglund, C.E. and Leib, D.A. (1995) BioTechniques 19:216-217;
	DG		Baumeister, R. et al.(1992)"Tet Repressor *Tet* Operator Interactions Derived From Mutants With New Recognition Specificities", *Structural Tools For The Analysis Of Proten-Nucleic Acid Complexes Advances In Life Sciences*, pp. 175-183;
	DH		Baumeister, R. et al.(1992)"Contacts Between Tet Repressor And *Tet* Operator Revealed By New Recognition Specificities Of Single Amino Acids Replacement Mutants", *Journal Of Molecular Boiology*, Vol. 226, pp. 1257-1270;
	DI		Baumeister, R. et al.(1992)"Functional Roles Of Amino Acid Residues Involved In Forming THE.Alpha.-helix-turn-.alpha.-helix operator DNA Binding Motif Of Tet repressor From Tn10", *Proteins: Structure, Function, and Genetics*, Vol. 14(2), pp. 168-177;
	DJ		Bradley, A., (1992)"Modifying The Mouse: Design And Desire", *Biotechnology*, Vol. 10, pp. 534-539;
	DK		Coghlan, A. "Gene dream fades away" *New Scientist* 148, pp. 14-15, (1995);
	DL		Crystal, R.G. "Transfer of Genes to Humans: Early Lessons and Obstacles to Success", *Science* 270, pp. 404-410 (1995);
	DM		Daddona et al., "Human Adenosine Deaminase." J. Biol. Chem. 259: 12101-12106(1984);
	DN		Damke, H. et al. "Induction of Mutant Dynamin Specifically Blocks Endocytic Coated Vesicle Formation." The Journal of Cell Biology 127 (4): 915-934;
	DO		Damke, H. et al. "Tightly Regulated and Inducible Expression of Dominany Interfering Dynamin Mutant in Stably Transformed HeLa Cells." Methods in Enzymology 257: 209-220 (1995);
	DP		Ebert, K.M. et al. (1988) "A Moloney MLV-Rat Somatotropin Fusion Gene Produces Biologically Active Somatotropin in a Transgenic Pig." *Molecular Endocrinology* 2(3): 277-283;
	DQ		Früh, K. et al., "Displacement of Housekeeping Proteasome Subunits by MHC-encoded LMP's: a Newly Discovered Mechanism for Modulating the Multicatalytic Proteinase Complex." EMBO Journal 13 (14): 3236-3244 (1994);
	DR		Früh, K. et al., "A Viral Inhibitor of Peptide Transporters for Antigen Presentation." Nature 375: 415-418 (1995);

Examiner	Date Considered

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		FILING DATE: 02/02/99	GROUP: 1632

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

	EA		Gunzburg, W.H. and Salmons, B. "Virus vector design in gene therapy", *Molecular Medicine Today* 1, pp. 410-417, (1995);
	EB		Hammer, R.E. et al. (1986) "Genetic Engineering of Mammalian Embryos." J. Anim. Sci. 63: 269-278;
	EC		Houdebine, L.-M. (1994)"Production of Parmaceutical Proteins From Transgenic Animals", *Journal Of Biotechnology* Vol. 34, pp. 269-287;
	ED		Kappel, C.A., et al., (1992)"Regulating Gene Expression In Transgenic Animals", *Current Opinion In Biotechnology*, Vol. 3, pp. 548-553;
	EE		Krimpenfort, P. et al. "Generation of Transgenic Dairy Cattle Using 'in vitro' Embryo Production." *BIO/Technology* 9, pp. 844-847 (1991);
	EF		Maheswaran, S. et al., "The WT1 Gene Product Stabilizes p53 and Inhibits p53-mediated Apoptosis." *Genes & Development* 9: 2143-2156 (1995);
	EG		Marshall, E. "Gene Therapy's Growing Pains" *Science* 269, pp. 1050-1055 (1995);
	EH		Mastrelangelo et al "Gene Terapy for Human Cancer: An Essay for Clinicians" *Seminars in Oncology* 23 (1), pp. 4-21 (1996);
	EI		Mendez, B. et al. "Heterogeneity of tetracycline resistance determinants" *Plasmid* 3 pp. 99-108 (1980);
	EJ		Muller, G., et al. (1995)"Characterization Of Non-Inducible Tet Repressor Mutants Suggests Conformaional Changes Necessary For Induction", *Nature Structural Biology*, Vol. 2(8), pp. 693-703;
	EK		Mullins, L.J. and Mullins, J.J. (1996) "Transgenesis in the Rat and Larger Mammals." J. Clin. Invest. 98(11) Supplement 1996: S37-S40;
	EL		Notarianni, et al., (1994)"Production of pharmaceutical proteins from transgenic animals", *Journal of Reproduction and Facility*, Vol. 41, pp. 51-56;
	EM		Orkin, S. H. and Motulsky, A.G. "Report and recommendations of the panel to assess the NIH investment in research on gene therapy" Dec. 7, 1995.
	EN		Pursel et al. "Genetic engineering of livestock" *Science* 244, pp. 1281-1288 (1989);
	EO		Salter, et al. "Transgenic chickens: insertion of retroviral genes into the chicken germ line" *Virology* 157, pp. 236-240 (1987);
	EP		Seamark, R.F. (1994) "Progress and Emerging Problems in Livestock Transgenesis: a Summary Perspective." *Reprod. Fertil. Dev.* 6: 653-657;
	EQ		Shan, B., et al., "Deregulated Expression of E2F-1 Induces S-Phase Entry and Leads to Apoptosis." *Molecular and Cellular Biology* 14(12): 8166-8173 (1994);
	ER		Sizemore, C. et al.(1990)"Quantitative Analysis of Tn*10* Tet Repressor Binging To A Complete Set Of *Tet* Operator Mutants", *Nucleic Acids Research*, Vol. 18(10), pp. 2875-2880;
	ES		Strojek, et al. (1988)"The Use Of Transgenic Animal Techniques For Livestock Improvement", *Genetic Engineering, Principles and Methods*, Vol 10, pp. 221-246;
	ET		Wall, R.J., (1996)"Transgenic Livestock:Progress and Prospects For The Future" *Theriogenology*, Vol. 45, pp. 57-68;
	EU		Wissmann, A., et al., (1991)"Amino Acids Determining Operator Binding Specificity In The Helix-Turn-Helix Motif Of Tn10 Tet Repressor", *The EMBO Journal*, Vol. 10(13), pp. 4145-4152;

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